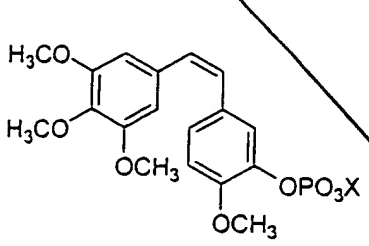
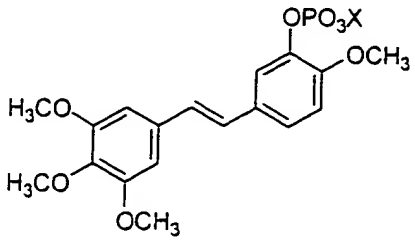
11. Combretastatin A-4 metal and ammonium phosphate prodrugs having the structure:



cis



trans

wherein [Y] X is selected from the group consisting of cesium, calcium, lithium, magnesium, manganese, zinc, imidazole, morpholine, piperazine, piperidine, pyrazole, pyridine, adenosine, cinchonine, glucosamine, quinine, quinidine, tetracycline, and verapamil.

REMARKS

Claim 9 has been amended, claim 11 has been added and claims 1-11 are in issue and do indeed replace original claims 1-9 as noted by the Examiner.

The Examiner's objections/rejections will now be addressed seriatim.

* * *

Item 1. The Examiner points out that the US application is based on a PCT and US provisional application. Applicant has amended the first statement of the Specification to adhere to this suggestion.

Item 2. The Examiner refers to two sets of claims. One which was originally filed with the PCT application and the second which were filed as amended. The Examiner is correct in presuming that the second set of claims which are the amended claims are the proper claims to be examined. The amended claims were received by the International Bureau on May 24, 1999 and includes claims 1-10. A new claim 11 has been added to clarify the scope of claim 9.

Item 3. The Examiner objects to the specification. On page 7 the formula should read $(R'O)_2P(NR^2)_2$ and replacement page 7 is enclosed for filing in this application.

Page 8. The definition of X=Z should be (divalent) and the obvious typographical error is corrected on the enclosed replacement page 8.

Regarding the Examiner's question pertaining pyridine and morpholine, note that the reactant is NH_2 plus the cation.

Item 4. No comment required.

Item 5. Applicants have reviewed your questions and report that both phosphate and sodium phosphate are correct. They also point out that the reason the examiner could not locate "*trans*-combretastatin A-4" in the outline search is that it is a totally new compound and that "combretastatin A-4" is only a *cis*-isomer. Further, applicants are not claiming to prepare a "racemic mixture" but rather a mixture of geometric isomers (*cis* and *trans*).

Further, in claim 1, the Examiner questions the location of the protective groups. The protective groups are on **both** the combretastatin A-4 ring **and** on the phosphite ester.

Regarding the "yield" in claim 1, the process creates all three products. It is believed that claim 1 as amended will resolve the Examiner's confusion. If not, please let me know.

Regarding the Examiner's question directed to claim 2, the applicants report that "/" means that the solvent for the dibenzyl phosphine is limited to "carbon tetrachloride".

Next the Examiner questions the language of claim 5. The claim is written to show the X attached to the combretastatin molecule is as intended.

Applicant has reviewed the Examiner's other criticism in view of 35 USC §112 and it is believed that the several objections have been overcome. If the Examiner still believes there are problems to address, she is cordially invited to call the undersigned counsel with her observations.

* * *

Claim 9 stands rejected under §102 as anticipated by Rathbone, Pettit and Pettit. Applicant has divided claim 9 into claims 9 and 11. Applicant submits that this amendment obviates the bases for this rejection, which can therefore be withdrawn.

In view of the foregoing, it is respectfully submitted that all of the Examiner's objections/rejections have been obviated/traversed and can be withdrawn, that claims can also be noted allowed, and that this application can be passed to issue. Early action to this end is respectfully requested and earnestly urged.

Respectfully submitted,

Richard R. Mybeck
Reg. No. 17,886

October 15, 2001
Post Office Box 5540
Scottsdale, AZ 85261-5540
480/483-1285
Fax 480/483-7452

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Box fee Amendment, Washington, D.C. 20231 on the date indicated below.

October 15, 2001

Richard R. Mybeck

Claims

1. The method of synthesizing combretastatin A-4 prodrugs as monosodium and *trans*-combretastatin A-4 prodrugs comprising:

admixing combretastatin A-4 with a phosphorylating agent to form a phosphate ester of combretastatin A-4 having protective groups thereupon;

selectively cleaving said phosphate ester protective groups with [iodotrimethylsilane to yield] a phosphoric acid derivative of combretastatin A-4; and

treating said phosphoric acid derivative of combretastatin A-4 with sodium methoxide to yield combretastatin A-4 Prodrug disodium phosphate, the combretastatin A-4 prodrug monosodium phosphate and/or a trans-isomer thereof as the ultimate product.

2. The method according to Claim 1 in which said phosphorylating agent is selected from the group consisting of dibenzyl phosphite/carbon tetrachloride, di-*tert*-butyloxy (N,N-diethylamido) phosphine, and bis[2-(trimethylsilyl)ethoxy]N,N-diisopropylamidophosphine.

3. The method of Claim 1 in which said cleaving agent is selected from the group consisting of: iodotrimethylsilane, trifluoracetic acid, and tetrabutylammonium fluoride.

4. The method of Claim 2 in which said cleaving agent is selected from the group consisting of: iodotrimethylsilane, trifluoracetic acid, and tetrabutylammonium fluoride.

5. The method of claim 1 in which the ultimate product consists of X-combretastatin A-4 3'-O-phosphate wherein "X" is selected from the group consisting of cesium, calcium, lithium, magnesium, manganese, sodium, potassium, and zinc.

6. The method of claim 1 in which the ultimate product consists of Y-combretastatin A-4 3'-O phosphate wherein "Y" is selected from the group consisting of imidazole, morpholine, piperazine, piperidine, pyrazole and pyridine.

7. The method of claim 1 in which the ultimate product is Z-combretastatin A-4 3'-O phosphate wherein "Z" is selected from the group consisting of adenosine, cinchonine, glucosamine, quinine, quinidine, tetracycline, and verapamil.

8. The method of synthesizing a trans-isomer of combretastatin A-4 Pro-drug comprising:

dissolving combretastatin A-4 in acetonitrite to form a solution;

cooling the solution to –25°F;

adding carbon tetrachloride to the cooled solution with stirring;

adding 4-dimethylaminopyridine and dibenzyl phosphate to the cooled, stirred solution and warm to room temperature;

extracting the solvent from said room temperature solution to provide 3'-O-Bis(benzyl) phosphoryl- 3, 4, 4', 5 - tetramethoxy-(E)-stilbene;

admixing chlorotrimethyl silane with said 3'-O-Bis(benzyl) phosphoryl- 3, 4, 4', 5 - tetramethoxy-(E) stilbene;

separating the solvent from the admixed solution with ethyl acetate to form an extract;

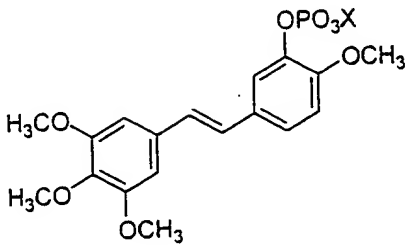
dissolving the extract in methanol;

adding sodium methoxide to said dissolved extract to form a second solution; and

removing the methanol from the second solution and recrystallizing the solid from

said second solution to form a trans-isomer of combretastatin A-4 prodrug.

9. Trans-combretastatin A-4 prodrugs having the structure

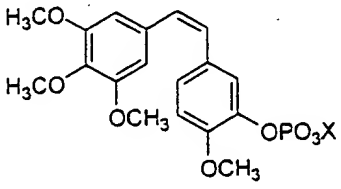


trans

wherein X is selected from the group consisting of cesium, calcium, lithium, magnesium, manganese, sodium, potassium, zinc, imidazole, morpholine, piperazine, piperidine, pyrazole, pyridine, adenosine, cinchonine, glucosamine, quinine, quinidine, tetracycline, and verapamil.

10. The method of claim 1 in which the ultimate product is recrystallized.

11. Combretastatin A-4 metal and ammonium phosphate prodrugs having the structure:



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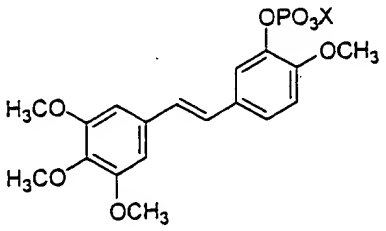

trans

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Claims

1. The method of synthesizing combretastatin A-4 prodrugs as monosodium and *trans*-combretastatin A-4 prodrugs comprising:

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4. The method of Claim 2 in which said cleaving agent is selected from the group consisting of: iodotrimethylsilane, trifluoracetic acid, and tetrabutylammonium fluoride.

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8. The method of synthesizing a trans-isomer of combretastatin A-4 Pro-drug comprising:

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cooling the solution to –25°F;

adding carbon tetrachloride to the cooled solution with stirring;

adding 4-dimethylaminopyridine and dibenzyl phosphate to the cooled, stirred solution and warm to room temperature;

extracting the solvent from said room temperature solution to provide 3'-O-Bis(benzyl) phosphoryl- 3, 4, 4', 5 - tetramethoxy-(E)-stilbene;

admixing chlorotrimethyl silane with said 3'-O-Bis(benzyl) phosphoryl- 3, 4, 4', 5 - tetramethoxy-(E) stilbene;

separating the solvent from the admixed solution with ethyl acetate to form an extract;

dissolving the extract in methanol;

adding sodium methoxide to said dissolved extract to form a second solution; and

removing the methanol from the second solution and recrystallizing the solid from

said second solution to form a trans-isomer of combretastatin A-4 prodrug.

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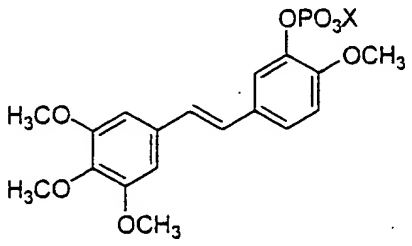

trans

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10. The method of claim 1 in which the ultimate product is recrystallized.

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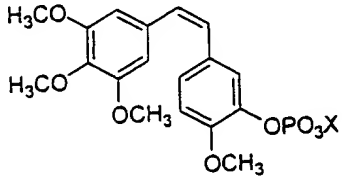
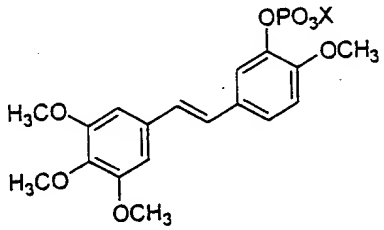


cis



trans

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